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Biomarkers and Oral Squamous Cell Carcinoma. An Update

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is a public health problem and the most common malignant neoplasm of the oral cavity. Oral cancer is associated with high mortality rates and considerable morbidity, which profoundly affects patients' quality of life. The identification and use of reliable biomarkers, such as α-SMA, E-cadherin, N-cadherin, CEA, EGF, CK19, or p53, have become crucial for early detection, accurate diagnosis, and effective monitoring of disease progression

and recurrence. Therefore, the present review aims to provide a comprehensive analysis of biomarkers used in the diagnosis of OSCC, covering their various applications, types, mechanisms of action, and use in OSCC-related research. A systematic search was performed in the MEDLINE (PubMed) and Web of Science electronic databases covering from January 1, 2015, to December 30, 2024. The search strategy was as follows: (α-SMA) AND ((epidermoid carcinoma) OR ((oral cancer) AND (oral squamous cell carcinoma))); for each of the selected biomarkers (alpha smooth muscle actin, E-cadherin, N-cadherin, carcinoembryonic antigen, epidermal growth factor receptor, cytokeratin 19, p53, Ki-67). The simultaneous use of multiple biomarkers could provide a more comprehensive understanding of the disease, enabling more accurate and specific diagnosis, prognosis, and treatment, ultimately improving patient outcomes and the clinical management of OSCC. This approach may help clinicians and researchers better understand the complexity of OSCC, enabling them to develop more effective strategies for early detection, disease monitoring, and personalized therapeutic interventions.

Keywords: Biomarkers, Oral cancer, Oral squamous cell Carcinoma, α-SMA, E-cadherina, N-cadherina, carcinoembryonic antigen, epidermal growth factor receptor, Citokeratin 19, p53, Ki-67.

INTRODUCTION

Oral cancer is a significant public health issue, with squamous cell carcinoma being the most prevalent malignant tumor of the oral cavity and oropharynx[1]. Oral squamous cell carcinoma (OSCC) accounts for 90–95% of all malignant tumors in the oral cavity[2]. The global incidence of oral cancer has increased; specifically, OSCC affects approximately 650,000 people each year and results in 350,000 deaths[3]. Due to its high morbidity and mortality, OSCC greatly impacts the quality of life of patients, either because of the tumor itself or by the effects of antineoplastic treatment[4].

Oral cancer ranks sixth among the most common cancers worldwide, with a mortality rate exceeding 50%[5]. The highest global rates are observed in developing countries in South and Southeast Asia, especially in India and Pakistan[6,7], where exposure to risk factors such as widespread tobacco and betel use is common. Globally, men are more affected by OSCC than women, at a ratio of 2:1[8]. However, in recent years, there has been a concerning increase in oral cancer cases among young adults and women[9,10], linked to lifestyle changes and exposure to traditional and emerging risk factors[11]. In Western countries, the most common sites of OCEC are the tongue edges, floor of the mouth, and oropharynx, whereas in South Asia, the oral mucosa and gingival-buccal complex are more frequently affected[12]. Tobacco use and its combustion products are the primary risk factors for OSCC and are responsible for most cases of OSCC[11]. Tobacco contains many carcinogens that cause genetic and epigenetic changes in the oral mucosal cells[13]. Genetically, carcinogens bind to DNA, forming adducts that distort the DNA helix and disrupt replication and repair, leading to mutations[14]. Epigenetically, tobacco use can cause abnormal DNA methylation, histone modifications, and changes in microRNA expression, which can silence tumor suppressor genes and activate oncogenes[15]. Regular alcohol consumption is also a significant risk factor, as it increases the permeability of the oral epithelium, acts as a solvent for tobacco carcinogens, and generates free radicals and acetaldehyde, which damage DNA. Combined exposure to tobacco and alcohol has a synergistic effect, significantly increasing the risk of OSCC[1].

Despite global anti-smoking campaigns and alcohol restrictions, a decline in the consumption of either substance is not expected in the near- to-mid-term. Therefore, reliable tools for the early diagnosis of OSCC and establishing its grade, which indicates behavior and progression, are crucial. In recent decades, the identification and utilization of reliable biomarkers for diagnosis, early detection, and monitoring of disease progression and recurrence has become an excellent approach. Biomarkers can potentially be applied clinically, not only for the early detection of primary tumors but also for recognizing recurrences and selecting therapeutic molecular targets[2]. In this narrative review, we examine current research on the significance of biomarkers in OSCC.

MATERIALS AND METHODS

Search strategy. A systematic search was performed in the MEDLINE (PubMed®) and Web of Science databases. The search period spanned from January 1, 2015, to December 30, 2024. The keywords used were derived from MeSH (PubMed®) terms: oral cancer, squamous cell carcinoma, oral squamous cell carcinoma, epidermoid carcinoma, biomarkers, α-SMA (alpha smooth muscle actin), E-cadherin, N-cadherin, CEA (carcinoembryonic antigen), EGF (epidermal growth factor receptor), cytokeratin 19, p53, and Ki-67. The search strategy was as follows: (α-SMA) AND ((epidermoid carcinoma) OR ((oral cancer) AND (oral squamous cell carcinoma))) for each selected biomarker.

EndNote X9.3.3 (Clarivate Analytics, Philadelphia, Pennsylvania, USA) was used to collect the identified citations and remove any duplicates. The titles and abstracts of each article were independently evaluated by two authors (IGS and DIRR). Articles were excluded if both reviewers considered them unsuitable based on their titles and abstracts. The full text was read to make a final decision in case of doubt.

RESULTS AND DISCUSSION

Biomarkers in OSCC

In recent years, there has been an increasing interest in identifying and applying biomarkers for the early diagnosis, prognosis, and monitoring of OSCC. Several definitions of biomarkers have been proposed. The most recent definition describes a biomarker as reagent with a measurable characteristic that can be evaluated objectively as an indicator of normal biological processes, disease processes, or responses to therapy[16]. Biomarkers can be derived from various sources, such as tumor tissue, blood, saliva, or other body fluids, and include genetic, epigenetic, proteomic, and metabolomic changes that reveal information about the biology and clinical progression of OSCC[17]. Finding and validating reliable biomarkers for managing OSCC is essential for more accurate and earlier diagnosis, guiding treatment choices, and predicting outcomes. Different categories of biomarkers have been studied for their potential in OSCC, including genomic, transcriptomic, proteomic, and epigenetic markers[18]. Some examples include smooth muscle alpha actin (α-SMA), E-cadherin, N-cadherin, carcinoembryonic antigen (CEA), epidermal growth factor receptor (EGFR), cytokeratin 19 (CK19), tumor suppressor p53, and the proliferation marker Ki-67. These biomarkers can offer valuable insights into the molecular

mechanisms of OSCC, supporting more precise diagnosis, personalized treatment approaches, and improved prognostic assessment.

Alpha-smooth muscle actin

Alpha-smooth muscle actin (α-SMA) is a cytoskeletal protein that has been studied as a potential OSCC biomarker. α-SMA is mainly expressed in myoepithelial cells and cancer-associated fibroblasts, and its expression has been linked to the invasive potential of OSCC[19]. Fibroblast differentiation into myofibroblasts is a vital step in tissue regeneration after injury. During this process, myofibroblasts actively participate in the stromal response to cancer cells, significantly enhancing the tumor's invasive and migratory abilities. Myofibroblasts, identified by the expression of smooth muscle alpha actin, play a crucial role in the tumor microenvironment, supporting the spread and invasion of malignant cells[20]. This stromal-epithelial interaction is a key component of the complex mechanisms underlying the progression and metastatic potential of OSCC. Several studies have shown that higher α-SMA expression correlates with poorer prognosis and increased metastasis risk in patients with OSCC[21]. Similarly, other studies have indicated that immunohistochemical detection of α-SMA can distinguish between benign and malignant oral lesions, emphasizing its potential as a diagnostic biomarker[22].

E-cadherin, and N-cadherin

E-cadherin and N-cadherin are cell adhesion molecules essential for epithelial-mesenchymal transition (EMT), a process that is key to cancer progression and metastasis[23]. E-cadherin serves as a major marker of the epithelial phenotype by maintaining cell-cell adhesion and tissue structure, whereas increased N-cadherin levels are linked to a more mesenchymal and invasive cell state[24]. The interaction between these two cadherins is a defining feature of EMT, where decreased E-cadherin and increased N-cadherin levels enable cancer cells to detach from the primary tumor, become more mobile, and infiltrate the surrounding extracellular matrix.

Several immunohistochemical studies have shown that the downregulation of E-cadherin and upregulation of N-cadherin are linked to increased tumor aggressiveness, higher rates of lymph node metastasis, and worse clinical outcomes in patients with OSCC[25]. Conversely, other studies have indicated that certain patterns involving HSP90, p53, and E-cadherin could act as potential independent prognostic biomarkers capable of predicting poor prognosis in OSCC[26]. This "switch" in cadherin expression is a vital step that facilitates the early stages of the metastatic process, enabling cancer cells to escape from the primary site and form secondary tumors in distant locations. Consequently, the dysregulation of E-cadherin and N-cadherin has been widely studied as a potential biomarker for the prognosis and treatment of OSCC[27].

Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA) is a glycoprotein typically expressed during fetal development that plays a role in cell-cell adhesion[28]. However, its expression is usually reduced in healthy adult tissue. Interestingly, elevated CEA levels have been observed in various cancers, including OSCC[29]. This increase in CEA levels may be linked to more advanced disease and a poorer

outlook for patients with OSCC. Additionally, some studies have reported higher CEA levels in both the saliva and serum of patients with OSCC. Moreover, it has been suggested that combining salivary biomarkers –such as Naa10p and CEA– enhances the diagnostic accuracy and early detection of OSCC[31]. These findings emphasize the potential of CEA as a useful biomarker for detecting, prognosticating, and treating head and neck cancer. Other studies[28] have investigated the diagnostic value of salivary ErbB2, a tyrosine kinase receptor involved in various cellular processes, alongside CEA for OSCC.

Epidermal growth factor receptor

The epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor that plays an essential role in the regulation of cell proliferation, survival, and invasion[32]. EGFR is often overexpressed in squamous cell carcinomas of the head and neck, particularly in HPV-negative cases[33]. However, the prognostic value of EGFR expression in predicting the risk of OSCC remains uncertain, as some studies have indicated that its expression is not always a reliable marker[34]. Despite this, EGFR overexpression or dysregulation has been linked to more aggressive disease, higher metastatic potential, and worse clinical outcomes in patients with OSCC[35]. Ongoing research is investigating the potential of EGFR-targeted therapies, such as tyrosine kinase inhibitors or monoclonal antibodies, for treating OSCC, especially in cases where EGFR overexpression drives tumor progression[36].

Cytokeratin 19

Cytokeratin 19 (CK19) is a type I intermediate filament protein commonly found in simple and stratified epithelial cells, including those of the oral cavity. Although the regulation of CK19 expression in cancers is still under investigation, previous reports suggest that it may act as a tumor suppressor in breast cancer but promote tumor growth in colon and liver cancers[37]. Interestingly, higher levels of CK19 have been detected in the saliva of patients with OSCC, indicating its potential as a non-invasive biomarker for the detection and monitoring of this disease[38]. Studies have shown that salivary CK19 levels are significantly elevated in patients with OSCC compared to healthy controls, with higher levels associated with more advanced disease stages[39]. However, the immunohistochemical expression of CK19 in OSCC varies depending on the degree of metastasis and tumor differentiation. While this biomarker could serve as a prognostic indicator, providing insights into tumor aggressiveness and clinical outcomes, its effectiveness as an independent diagnostic tool remains under discussion[40].

p53

p53 is a tumor suppressor protein that is crucial for regulating cell cycle progression, apoptosis, and maintaining genomic stability[41]. The p53 gene is often mutated in various cancers, including OSCC, resulting in the accumulation of mutant p53 proteins that can be detected in tumor cells[42]. Known as the *"guardian of the genome"* p53 functions as a critical gatekeeper that prevents the growth of cells with DNA damage or genomic instability. However, the role of p53 in the development and progression of oral cancer remains complex and multifaceted[43].

Inactivation or mutation of p53 is a common event in the development of OCC and has been widely studied as a potential biomarker for this disease[44]. Overexpression of the mutant p53 protein, usually caused by mutations in the TP53 gene, has been linked to more aggressive tumors, increased lymph node metastasis, and worse clinical outcomes in patients with OSCC. This is because mutant p53 cannot effectively suppress tumor growth or progression[42]. However, the relationship between p53 status and prognosis in OSCC is not always clear, as some studies have failed to find a consistent relationship between p53 expression and disease outcomes[45]. This indicates that the potential of p53 as an independent biomarker for OSCC may be limited and highlights the need for further research to better understand its role in this disease. Combining p53 analysis with other molecular markers could enhance its diagnostic and prognostic usefulness, offering clinicians comprehensive information to support treatment decisions and patient management.

Ki-67

Ki-67 is a well-known marker of cell proliferation, as its expression is closely correlated with cell cycle progression[46]. In the context of OSCC, many studies have explored Ki-67's potential as a biomarker for disease detection, prognosis, and treatment response. Ki-67 overexpression has consistently been found in OSCC tumor samples compared to normal oral mucosa, indicating its usefulness as a diagnostic marker for OSCC[47]. Additionally, Ki-67 expression level has been linked to several clinicopathological features, such as tumor size, lymph node metastasis, and disease stage, suggesting its potential as a prognostic indicator. Some studies have shown that high Ki-67 levels are associated with worse prognosis and lower overall survival in patients with OSCC, emphasizing its role as a marker of tumor aggressiveness[48]. However, the clinical relevance of Ki-67 as a biomarker for OSCC remains debated because its expression does not always correlate with disease outcomes[49]. Factors such as assessment methods, cutoff values used to distinguish high from low expression, and the heterogeneity of OSCC tumors may contribute to the varied results reported in the literature. Despite these challenges, evaluating Ki-67 expression, both alone and alongside other molecular markers, can still offer valuable information to clinicians regarding tumor proliferation and help guide the choice of appropriate therapy.

Although EGFR overexpression or dysregulation, elevated CK19 levels, and changes in p53 and Ki-67 have been linked to various aspects of OSCC, their usefulness as standalone biomarkers is controversial. The relationship between these molecular markers and disease outcomes is often complex and multifaceted; thus, further research is needed to fully understand their role in the diagnosis, prediction, and management of OSCC. Combining these biomarkers with other molecular and clinicopathological factors could provide more comprehensive information to help healthcare professionals make better decisions and improve patient care.

CONCLUSION

The significance of biomarkers in the diagnosis, prediction, and management of OSCC cannot be overlooked. Many studies have examined the potential of different molecular markers, including EGFR, CK19, p53, and Ki-67, as tools for the diagnosis and prognosis of this disease. Although the overexpression or dysregulation of these markers has been linked to various

clinicopathological features and disease outcomes, their value as standalone clinical indicators remains debatable. The connection between these biomarkers and OSCC is often complex, with factors such as tumor heterogeneity, assessment methods, and cutoff points possibly explaining the differing results reported in research.

Looking ahead, integrating multiple biomarkers with other clinical and pathological data could provide a more comprehensive approach to the personalized diagnosis, prognosis, and treatment of OSCC. Ongoing research in this area will be vital to further clarify the role of biomarkers in this disease and develop more robust and clinically useful tools for guiding patient management.

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